GENERAL PRACTICE IN CHINA

Advances in the Application of Autologous Platelet Concentrate in the Field of Gynecology

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Recommended Citation

WANG X X, MAO L L,WANG Z J, et al. Advances in the Application of Autologous Platelet Concentrate in the Field of Gynecology[J]. Chinese General Practice, 2023, 26（35）: 4472-4476,4482.

DOI: 10.12114/j.issn.1007-9572.2023.0213.

Available at: https://gpinchina.net

Advances in the Application of Autologous Platelet Concentrate in the Field of Gynecology

WANG Xiaoxue, MAO Lele, WANG Zijun, YANG Mukun, BAI Wenpei, DIAO He

【**Abstract**】 Autologous platelet concentrate（APC）is a platelet concentrate obtained by centrifugation of human or animal blood, mainly includes first-generation platelet concentrate platelet-rich plasma（PRP）and second-generation platelet concentrate platelet-rich fibrin（PRF）, which is widely applied in varies fields such as dental implants, bone defect repairing and burn plastic surgery because of its role in wound healing and tissue repair. In recent years, autologous platelet concentrate has been applied to improve ovarian function, promote the repair of endometrial hyperplasia, treat cervical and vulvo-related lesions, and has achieved significant efficacy. However, there is a lack of effective integration of PRP and PRF research results in the field of gynecology. This paper systematically and comprehensively review the preparation, biological properties and applications in various gynecological diseases, in order to provide clinicians with new treatment ideas for gynecological diseases and reference for the further application of APC.

【**Key words**】 Gynecologic diseases；Platelet-rich plasma；Platelet-rich fibrin；Autologous platelet concentrates；Endometrial hyperplasia；Ovarian diseases；Review

Platelets are derived from mature megakaryocytes of bone marrow, which agglutinate into clusters to initiate hemostasis when tissue trauma is hemostatic, while platelets contain a large number of particles in the cytoplasm, and after activation of platelets and degranulation of particles, they release a large number of growth factors related to wound healing and regeneration and repair of tissues, promoting cell proliferation and migration[1-3]. Autologous platelet-rich concentrate is a high concentration platelet concentrate obtained by centrifugation of human or animal whole blood, and its platelet content is 4~5 times higher than that of whole blood[4], which plays an important role in wound healing, tissue repair and regeneration.

Autologous platelet-rich concentrates mainly include the first-generation platelet-rich plasma （PRP） and the

second-generation platelet-rich fibrin （PRF）, which are widely used in the fields of oral implantation[5-6], bone defect repair[7], burns cosmetic surgery[8] and other fields. In recent years, autologous platelet-rich fibrin concentrate has been used in gynecological fields such as endometrial, cervical and vulvar lesions, and has achieved remarkable efficacy. However, gynecologists have limited knowledge of this, so this article provides a review of the progress of the application of autologous platelet-rich concentrates in gynecological diseases, in order to provide clinicians with new diagnosis and treatment of gynecological diseases, and to provide a reference for the in-depth development of the research and application of autologous platelet-rich concentrates.

1 Literature search strategy

PubMed, Web of Science, Embase, and China Knowledge Network （CNN） databases were searched from inception to February 2023 by computer. The English search terms included "platelet-rich plasm", "platelet-rich fibrin", "PRP", "PRF" and "Gynecological". Chinese search terms include "autologous platelet-rich plasma concentrate "platelet-rich fibrin" "PRP" "PRF" "Gynecological diseases". Inclusion criteria: clinical or basic studies, reviews, meta-analyses, case reports on the preparation, biological characterization, and treatment of autologous platelet-rich plasma concentrates or PRP or PRF. Exclusion criteria: conference abstracts, reviews, reply letters, and literature of unavailable full text and poor quality.

2 PRP-related studies

2.1 Preparation methods of PRP Platelet-related products appeared in the 1870s, and platelet concentrates gained wide attention with the emergence of PRP extraction technology in the 1990s[9]. PRP is a highly concentrated platelet plasma obtained by centrifugation of autologous whole blood, and its content of growth factors is 5-10 times that of whole blood. PRP is mainly obtained by gradient-density centrifugation, which mainly includes one-step centrifugation, two-step centrifugation and three-step centrifugation. PRP is mainly obtained by gradient density centrifugation, which mainly includes one-step centrifugation, two-step centrifugation and three-step centrifugation. Two-step centrifugation is widely used in clinic because of its high platelet concentration and high growth factor yield[10], and the main steps are as follows[11]: （1） draw venous blood and inject it into test tubes containing anticoagulant; （2） in order to prevent platelets from being activated during centrifugation, the recommended centrifugation temperature is 21~24 ℃, and after centrifugation with a certain centrifugal force, the blood is divided into three layers, the bottom red blood cell layer accounts for about 1/2 of the total volume of blood, the thin white

layer in the middle is rich in leukocytes, and the top platelet layer contains a small amount of leukocytes in yellow color; （3） the plasma above the red blood cell layer is sucked up with a pipette and injected into another sterile tube without anticoagulant; （4） the plasma after centrifugation is divided into two layers, the upper 2/3 of which is the platelet-poor plasma, and the lower 1/3 of which is the platelet-rich plasma. 30 mL of venous blood can produce 3~5 mL of PRP; （5） Remove the upper layer of platelet-poor plasma with a pipette and leave enough plasma to suspend the platelet-enriched plasma, add bovine thrombin and calcium chloride to activate the platelets, and then it can be used in the clinic. With the application and development of PRP technology, PRP commercial preparation systems have begun to be utilized in the clinic.

2.2 Structural and biological characteristics of PRP PRP is a red viscous liquid to the naked eye, and under scanning electron microscopy, platelets can be seen to aggregate into clusters stacked on top of each other, with a large number of pseudopods sticking out, and some leukocytes dispersed in the platelets[12]. Platelets in PRP are enriched with a large number of cytokines and growth factors. Growth factors, insulin-like growth factor, vascular endothelial growth factor, platelet-derived angiogenic factor, transforming growth factor β, fibroblast growth factor, epidermal growth factor, connective tissue growth factor, and interleukin 8 are released from platelets once they are activated[13]. In addition to growth factors, platelets can also secrete other substances such as fibronectin, hyaluronan, and sphingosine 1-phosphate, which promote wound repair and tissue regeneration by promoting cell chemotaxis, cell adhesion, cell proliferation, cell migration, and angiogenesis[14]. PRP, with a pH value of 6.5-6.7, is a weakly acidic medium that inhibits microorganisms, and at the same time, platelets can secrete bactericidal proteins that, when activated, can also be used to inhibit microorganisms. At the same time, platelets can secrete bactericidal proteins and release some antimicrobial peptides when activated[15]. Therefore, PRP can exert antimicrobial effects from various aspects.

2.3 Basic research on PRP in gynecological diseases

2.3.1 Promotion of endometrial cell proliferation and endometrial repair SUGINAMI et al [16-17] analyzed the distribution pattern of platelets during the human menstrual cycle by means of immunohistochemistry and found that, in the endometrial stroma close to the luminal epithelium, platelets were distributed more during the menstrual phase, and less during the proliferative and secretory phases.

When platelets were cultured with EM-E6/E7/hTERT endometrial epithelial immortalized cells, it was found

that platelets promoted the adhesion of EM-E6/E7/hTERT cells to the stromal gel and increased cell-cell contact by promoting the expression of E- calreticulin, which suggests that platelets may be involved in the re-epithelialization of human endometrial cells. AGHAJANOVA et al[18] found that activated 5% PRP promoted the migration of human endometrial mesenchymal fibroblasts, endometrial mesenchymal stem cells, and bone marrow-derived mesenchymal stem cells, as well as the proliferation of human endometrial mesenchymal fibroblasts and endometrial mesenchymal stem cells. These two studies provide in vitro evidence that platelet concentrates promote endometrial regeneration and repair. In animal studies, intrauterine injection of PRP can promote the regeneration of ethanol-induced endometrial injury in rats and reduce endometrial fibrosis and increase endometrial tolerance[19]. ZHANG et al[20] studied the synergistic therapeutic effect of PRP on the stromal cells derived from menstrual blood on the mechanical injury of uterine adhesion and found that PRP can enhance the repairing effect of stromal cells derived from menstrual blood on the endometrial lining. It was found that PRP could enhance the repairing effect of menstrual blood-derived stromal cells on the endometrium. The above study provides evidence that PRP can be used clinically to improve the function of the endometrium.

2.3.2 Protecting ovarian function from injury In order to study the protective effect of PRP on ovarian ischemia/reperfusion injury, BAKACAK et al[21] conducted the uterine adnexal torsion injury experiment with 60 female rats. The experimental group was injected intraperitoneally with PRP 30 min before torsion, and after torsion was lifted, the experimental group was better than the control group in terms of the level of oxidative stress, histopathological changes and reduction of ischemia/reperfusion injury in the ovary. After the torsion was released, the experimental group showed better oxidative stress level, histopathological changes and reduction of ischemia/reperfusion injury in the ovary than the control group, suggesting that PRP can protect the ovary function from ischemia/reperfusion injury.

2.4 Clinical application of PRP in gynecological diseases

2.4.1 Promote healing of postoperative wounds after gynecological surgery and reduce complications After activation of platelets in PRP, it releases a variety of high-concentration growth factors, which is far more than the threshold of growth factor concentration needed for wound repair, and it can rapidly initiate wound repair, promote the proliferation, migration, extracellular matrix deposition and regeneration of local blood vessels of local repair cells, and have significant efficacy in the healing of diabetic chronic wounds, decubitus ulcers, TEHRANIAN et al[24]

studied the effect of autologous PRP on wound healing in women with high-risk cesarean section, 140 patients were randomly divided into two groups, the intervention group was given PRP treatment after operation, and the control group was given routine care, and the results showed that the redness, ecchymosis and pain in the PRP group decreased more significantly than that in the control group. The results showed that redness, swelling, ecchymosis and pain decreased more significantly in the PRP group than in the control group, and the difference was statistically significant （P<0.001）, suggesting that PRP can accelerate the healing of refractory wounds after cesarean delivery. Another phase I/II prospective study was conducted to evaluate the safety and efficacy of PRP in gynecological surgery. A total of 55 consecutive patients who underwent gynecological surgery were enrolled, and 20 mL of PRP was administered directly to the surgical site after the surgery; compared with the control group, the pain score in the PRP group was lower （2.7 vs. 6.7, P<0.001）, the morphine dosage was less （17 mg vs. 26 mg, P <0.05）, and no adverse effects occurred[25]. MEDEL et al[26] found that the use of platelet gel prior to vulvar reconstruction was an effective strategy for preventing wound rupture after surgery for locally advanced vulvar cancer; the study divided patients undergoing surgery for vulvar cancer （radical vulvovaginal surgery） into group A （n=10） and group B （n=15）, with platelet gel placed in the vaginal area of the cleft during the reconstructive surgery in group A and only in group B. Group A placed platelet gel in the vaginal fissure at the time of reconstructive surgery, and Group B underwent surgery only to assess the efficacy of platelet gel application after radical surgery in women. The efficacy of applying platelet gel after radical female surgery was evaluated; the rates of wound infection, vaginal wound necrosis and wound disintegration in Group A were significantly lower than those in Group B （P<0.05）; the incidence of postoperative fever in Group A was significantly lower than that in Group B, and the postoperative hospitalization time was significantly shorter and wound healing speed was significantly faster （P<0.05）.

2.4.2 Treatment of vulvar and cervical lesions BEHNIA-WILLISON et al[27] studied the therapeutic effect of PRP on glucocorticoid-resistant vulvar sclerosing tundra, patients received three vulvar injections of PRP at intervals of 4~6 weeks, and then received PRP again after 12 months; 28 patients showed clinical improvement in the size of the lesions, among which 28.6% of the lesions completely disappeared after PRP treatment. HUA et al[28] carried out a randomized clinical study of PRP and laser treatment of benign cervical lesions, the results showed that the re-epithelialization time of the PRP group was significantly shorter than that of the laser group, and the incidence of adverse reactions was significantly lower than that of the laser group.

2.4.3 Improvement of ovarian function and ovarian responsiveness in in vitro fertilization Ovarian reserve function is an important index for evaluating female fertility, but poor ovarian responsiveness and low fertilization rate due to age factor in ovulation promotion is still a difficult problem in the field of female fertility preservation. White et al[29] showed that intravitreal injection of platelets containing growth factors may promote the recovery of oocytes in the ovary. CAKIROGLU et al[30] performed PRP intra-ovarian injection on 311 women aged 24-40 years with primary ovarian insufficiency, and found that PRP could increase serum antimullerian hormone values and improve female fertility; 7.4% of women could conceive naturally after PRP injection, and 64.8% of women showed dominant follicles and attempted in-vitro fertilization, of which 82 （26.4%） were successful in fertilization. Subsequently, CAKIROGLU et al[31] performed PRP intra-ovarian injections in 474 women aged 30-45 years with a history of poor ovarian response （POR）, and 65.8% of the women had successful in vitro fertilization of their eggs and underwent embryo transfer. The abundant blood supply and platelet-derived cytokines are important factors for normal ovarian function, and the large amount of cytokines in PRP may have promoted the neovascularization and cellular activation in the ovary, thereby improving ovarian responsiveness and female fertility.

2.4.4 Promote endometrial regeneration and repair to improve pregnancy outcome The endometrium is crucial for embryo implantation and pregnancy maintenance, and endometrial repair disorders caused by various reasons of endometrial basal layer damage are an important cause of uterine infertility and pregnancy complications. The current therapeutic approaches to promote endometrial regeneration, estrogen[32] and stem cells[33], still have their limitations. CHANG et al[34] and COLOMBO et al[35] studied five cases of in vitro fertilized women with poor endometrial response, in which the endometrial thickness was still <7 mm after the standard hormone replacement therapy, however, 0.5-1.0 mL of PRP was injected into the uterine cavity on the 10th day of menstruation in conjunction with conventional sex hormone therapy, and it was found that PRP could promote the growth of the endometrium, and pregnancy was successfully achieved in five patients.

COLOMBO et al[35] used PRP in patients who had been treated with three classical drug regimens, but the endometrial thickness was still <6 mm, which led to the cancellation of the transfer cycle, and found that 87% of the patients had a significant increase in endometrial thickness before progesterone injection and embryo transfer. In the studies of CHANG et al[36] and DOGRA et al[37], endometrial thickness, clinical pregnancy rate, and cycle cancellation rate of the PRP group were better than those of the control group. NAZARI et al[38] reported that in 18

patients with previous recurrent implantation failures, the patients were injected with 0.5 mL of PRP into the uterine cavity 48 hours prior to the transfer of the embryos and showed that, except for two early miscarriages, 16 out of 18 patients had successful pregnancies that developed successfully up to the end of the observation period. In a subsequent randomized controlled study, 138 patients who failed to conceive after 3 or more high-quality embryo transfers were included, 0.5 mL of PRP was injected intrauterinely 48 h before blastocyst transfer in the PRP group, and the control group was given the standard treatment, and the clinical pregnancy rate in the PRP group （44.89%） was much higher than that in the control group （16.66%） （P<0.05）[3]. It can be seen that PRP has significant efficacy in patients with thin endometrium, repeated implantation failure due to uterine factors and uterine adhesion, which can not only increase the thickness of the endometrium but also improve the function of the endometrium, and provides a new therapeutic means in the field of reproduction.

3 PRF-related studies

3.1 Characteristics of PRF PRF is a platelet concentrate obtained by centrifugation of venous blood, and it is the second generation of autologous platelet concentrates, which was discovered by DOHAN et al[2] in 2006. PRF has the following advantages over PRP: （1） it is easy to make, requires only one centrifugation, and does not need to be activated by prothrombin in the process of preparation without the addition of an anticoagulant; （2） it is a loose mesh structure of three-dimensional dimensions in which platelets and growth factors network together, and the platelets and growth factors network together; （3） PRF is rich in fibronectin, which itself can cover the wound and promote wound healing, and studies have reported that the PRF matrix contains glycosaminoglycans （heparin, hyaluronic acid）, which have a strong affinity for circulating small polypeptides, and the fibronectin matrix stimulates the expression of the integrin avb3, so that PRF has a strong ability to support cell migration and healing[39].

3.2 Clinical application of PRF in gynecological diseases Currently, PRF has significant efficacy in promoting alveolar bone regeneration, cranial bone repair, and corneal repair[40-41], but the study of PRF in the field of gynecology is relatively rare. In pelvic reconstruction surgery, vaginal grafts, whether resorbable or non-resorbable, have serious adverse effects. GORLERO et al[42] carried out a prospective observational study to evaluate the effect of PRF on the repair of vaginal prolapse surgery. Ten patients requiring surgical repair and with high risk of recurrence factors （degree II or higher） were treated with PRF at the surgical site, and it was found that the recovery rate of anatomical structures was 80%, the recovery rate of the prolapse was 80%, and the recovery rate of the prolapse was

20%. In 10 patients who required surgical repair and had high risk of recurrence factors （degree II or higher）, PRF was given at the surgical site and found that the anatomical structure was restored by 80%, the symptoms of prolapse were improved by 100%, the sexual activity was increased by 20%, and there was no pain in sexual intercourse, with no intraoperative or postoperative complications. SHIRVAN et al[43] found that autologous PRP combined with PRF is a new minimally invasive treatment for genital fistula. It was found that 11 patients were clinically cured and had normal transvaginal physical examination and cystography.

WANG et al[44] found that the pregnancy rate of patients in the PRF group was significantly higher than that of the non-treated group, and the score of uterine adhesions was significantly lower than that of the pre-treatment group, which indicated that PRF had a better effect on promoting endometrial repair and reducing the re-formation of uterine adhesions. Yang Mukun et al[45] analyzed the endometrial tissues of patients with uterine adhesions treated with PRF and found that the number of endometrial glands, the expression of Ki67, cytokeratin 18 and waveform protein increased and the fibrotic area was significantly reduced compared with the preoperative area after PRF treatment. This suggests that PRF may promote wound repair by promoting endometrial gland proliferation and inhibiting fibrosis.

4 Summary and outlook

Autologous platelet-rich concentrates （PRP） are derived from the body itself, avoiding allergic reactions, cross-infections and immune rejection in the process of use, and its high concentration of growth factors has a broad application prospect in promoting wound healing and tissue regeneration. PRP and PRF have been prominently used in gynecological diseases, such as promoting the regeneration and repair of the endometrium in uterine adhesions, and improving pregnancy outcomes, and improving ovarian function and ovarian responsiveness in in-vitro fertilization. PRP and PRF are more prominent in gynecologic diseases by promoting endometrial regeneration and repair in uterine adhesions, improving pregnancy outcomes, ovarian function and responsiveness in IVF.

Both PRP and PRF play an important role in two of the most difficult issues affecting female fertility, demonstrating a strong potential for fertility protection. However, the research of autologous platelet-rich plasma concentrates in gynecology has the following problems: （1） more in-depth basic research is needed to elucidate the mechanism of PRP and PRF in promoting wound healing and tissue regeneration; （2） the mechanism of PRP and PRF in gynecology should be clarified. The use of PRP and PRF in gynecology is still in its infancy, and the

current research is mainly based on case reports and retrospective studies, with a low level of evidence. Large-scale, multicenter, high-quality randomized controlled studies are needed to further validate the safety and efficacy of PRP and PRF in the near and long term; （3） there is an urgent need to formulate the specifications for the application of PRP and PRF, including the preparation method, application process, quality control, application dosage, and the use of PRP and PRF.

Authors' contributions: Wang Xiaoxue and Bai Wenpei were responsible for proposing the study; Wang Xiaoxue was responsible for writing the paper; Mao Lele was responsible for collecting and screening the literature; Wand Zijun, Yang Mukun, and Diao He were responsible for revising the paper; and Bai Wenpei was responsible for the revision of the final version, the quality control of the article, and the proofreading of the article, and was responsible for the paper.

There is no conflict of interest in this paper.

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